WHO NRA strengthening programme: oversight of clinical trials, expected standards and challenges for vaccine regulation including prequalification

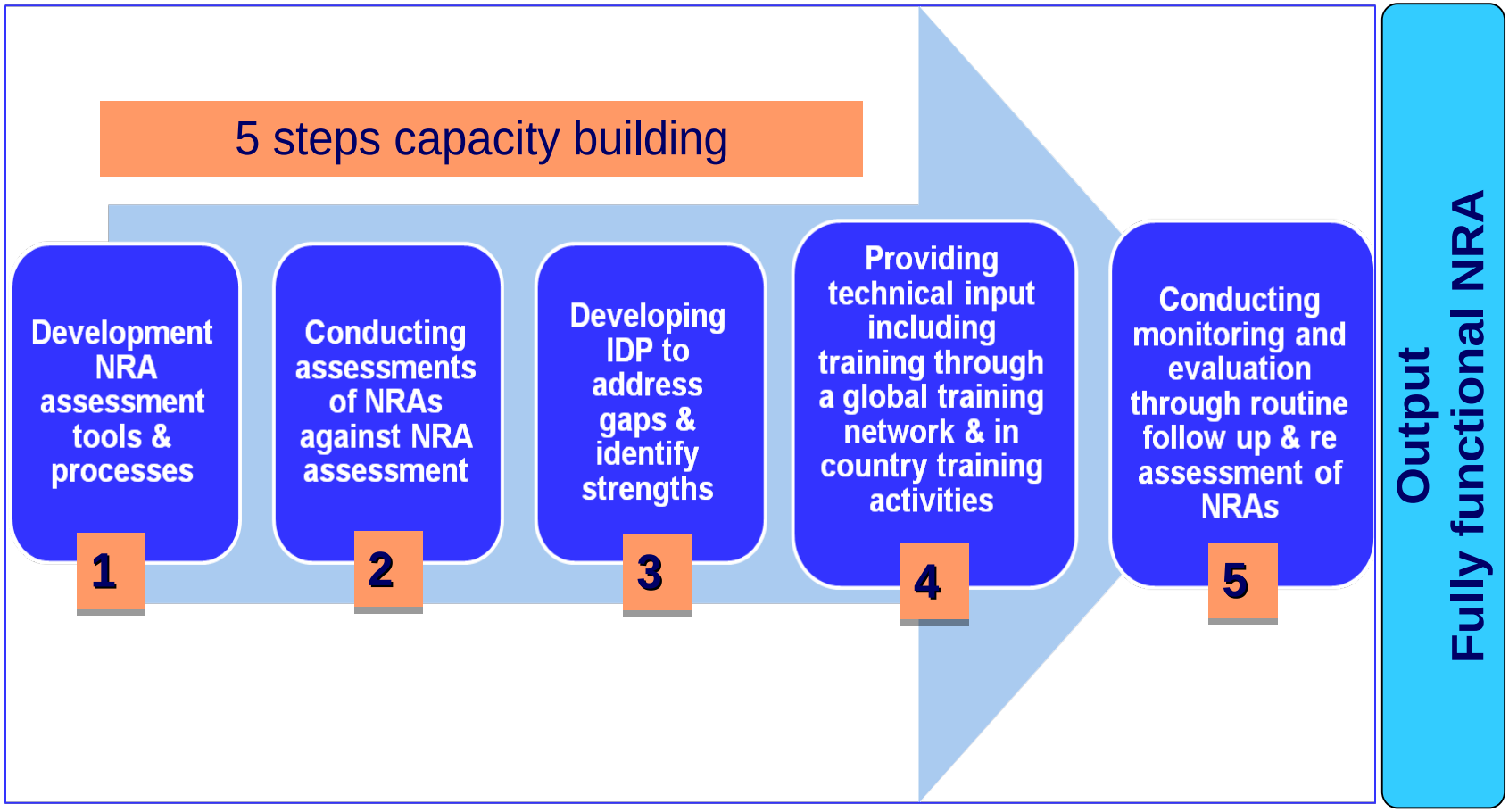
Lahouari Belgharbi, Scientist,
WHO HQ, Geneva

World Health Organization

Outline of the presentation

1. WHO NRA strengthening programme:
   - Global overview of regulation of clinical trials
   - expected standards for regulation of vaccines clinical trials
   - WHO vaccine prequalification: expectations
2. Discussions

WHO NRA strengthening activities



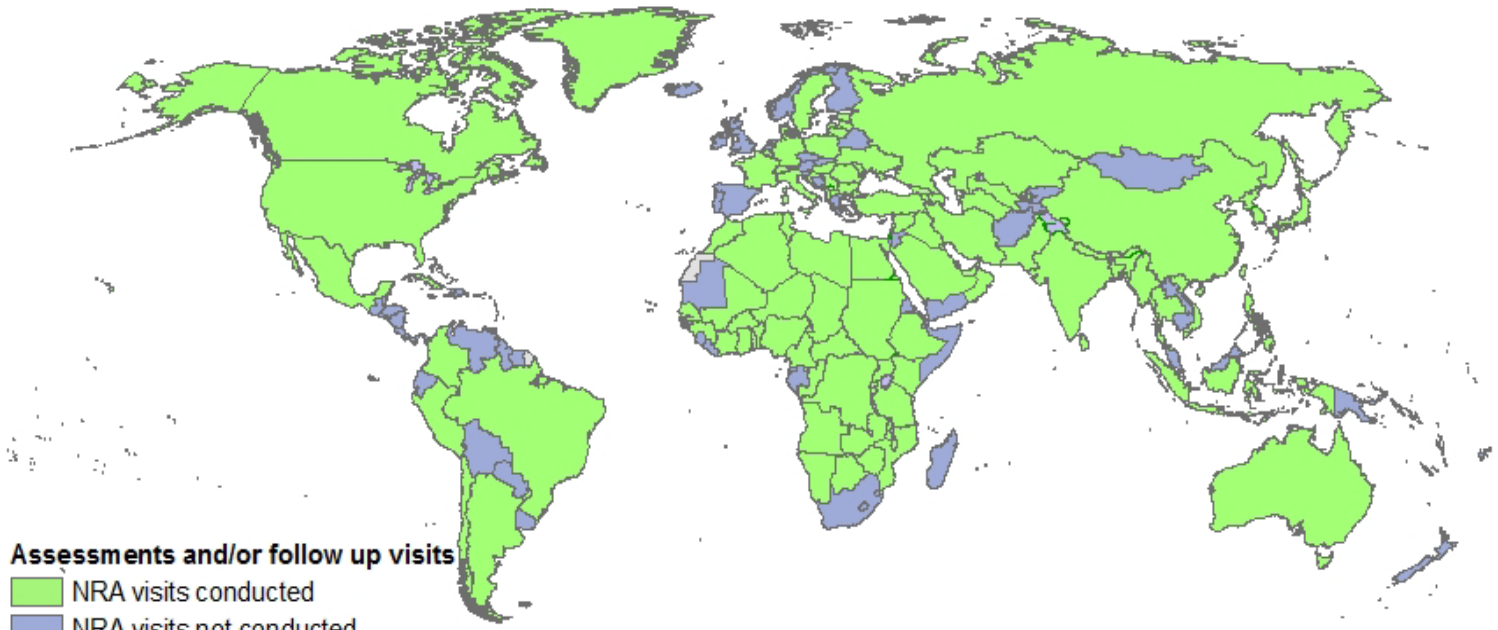
World Health Organization/Immunization, Vaccines and Biologicals (IVB), as of May 2011

World Health Organization

Regulatory oversight of clinical trials

Indicators to monitor regulatory function performance
CT01: System for regulatory oversight of clinical trials (CTs)
CT02: Quality Management System for oversight of clinical trials activities by NRA
CT03: Human resource management
CT04: Format and content for submission of clinical trials application
CT05: Assessment of clinical trials application
CT06: Assurance of ethical oversight

WHO NRA Assessment visits
2011: 97 countries assesed through 185 visits



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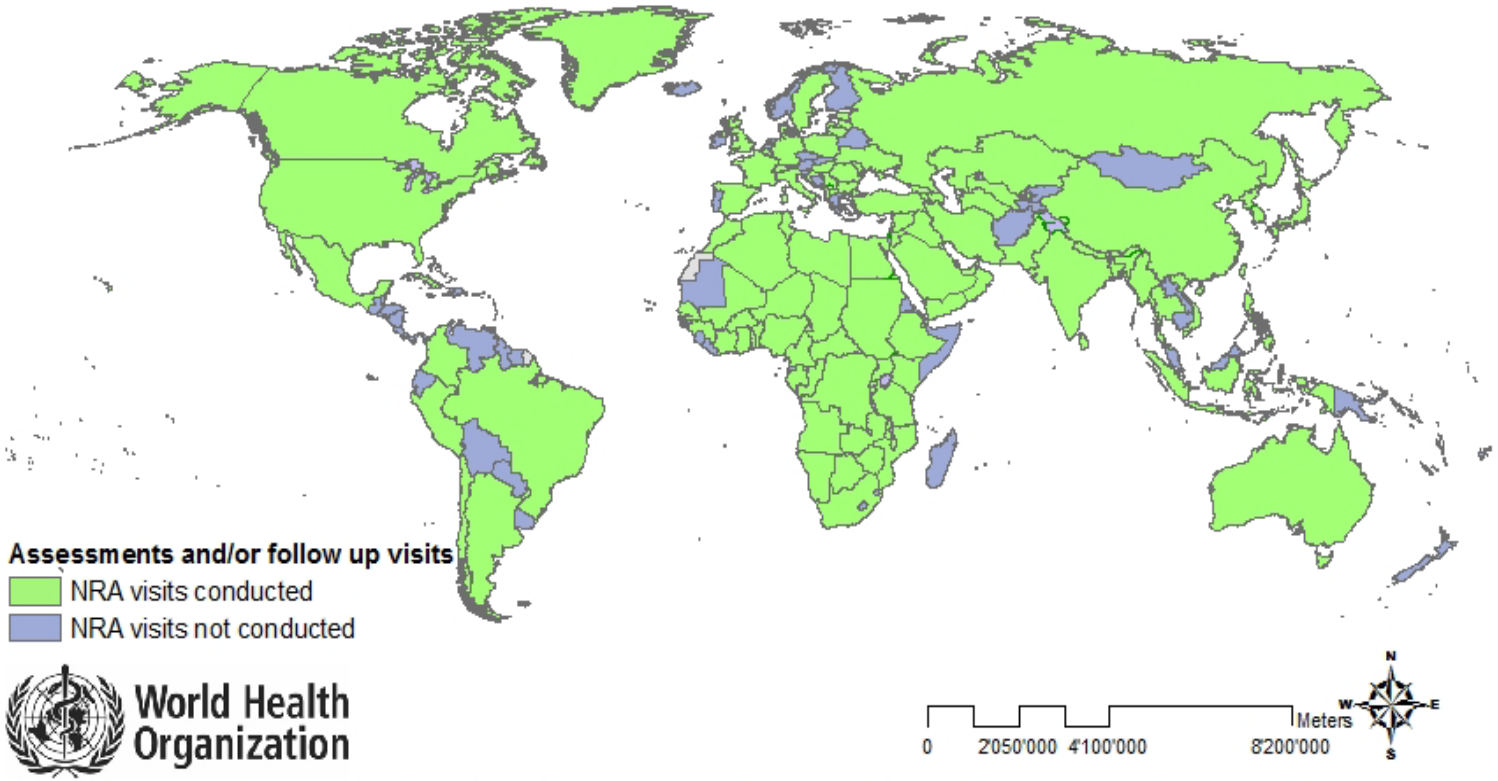
Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: World Health Organization, Immunization Vaccines and Biologicals (IVB). Updated as of 21 November 2011
Map Production: Public Health Information and Geographic Information Systems (GIS) World Health Organization in collaboration with P&B Consulting

World Health Organization/Immunization, Vaccines and Biologicals (IVB), as of Nov 2011

World Health Organization

WHO NRA Assessment visits & Follow up 2011: 537 visits conducted for 106 countries



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**The Global Alliance for Vaccines and Immunisation

World map image: http://hubpages.com/hub/Free_World_Map

World Health Organization/Immunization, Vaccines and Biologicals (IVB), as of Nov

World Health Organization

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Regulatory oversight of clinical trials : WHO vaccine prequalification expectations

Indicators to monitor regulatory function performance
CT01: System for regulatory oversight of clinical trials (CTs) - **Critical**
CT02: Quality Management System for oversight of clinical trials activities by NRA - **Critical**
CT03: Human resource management- **Critical**
CT04: Format and content for submission of clinical trials application- **Critical**
CT05: Assessment of clinical trials application- **Critical**
CT06: Assurance of ethical oversight- **Critical**

For the design of a clinical trial to be valid, it must comply with the following four requirements:

Validity

1. commitment to **ethical** guidelines, **patient safety** and **GCP**;
2. **scientific** and **medical validity**;
3. **methodological** validity and absence of **bias**;
4. **feasibility.**

Reading protocol

- The protocol **describes** the objectives, methodology, design, statistical considerations and organization of a trial.
- gives a **justification and guarantees** to be met for conducting the trial, but this information may be in a separate document referred to in the protocol.
- **Reading a protocol** is important for guaranteeing the safety of patients who will take part in the trial but also to ensure that the results of the trial will be **relevant and usable**.
- This document is **a reading guide** which sets out the questions which should be asked when making a **critical evaluation** of a trial.

Commitment to ethical guidelines and patient safety

Regulatory concern is whether:

- . the proposed trial offers all the ethical guarantees?
- . the subjects who will take part are likely to obtain a therapeutic benefit or, on the contrary, whether they risk a loss of opportunity in relation to known treatments?

I should review the following information

1. **Evaluation of the project by an Ethics Committee?**
2. **Patient information and consent?**
3. **Confidentiality and protection of medical data?**
4. **Will a patient who takes part in the trial suffer loss of opportunity?**
   - **Product safety**
     a) Adequate pharmaceutical quality and design
     b)Suitable non-clinical prerequisites?
   - **Demonstrated or expected efficacy**
   - **Risk / benefit balance and constraints for patients**
   - **Monitoring efficacy and tolerance during the trial**
   - **Follow-up and treatment of patients after the trial (study treatments + others)**

Scientific and medical validity

Regulatory concern is whether:

- has the trial previously been conducted?
- are the patients in the trial similar to the population exposed to the disease?
- is the treatment and follow-up of patients appropriate in the context?

I should review the following information

1. Are the scientific value of the trial and its rationale satisfactory (in particular, avoid repeating a trial previously conducted, etc.)?
2. Are the inclusion and non-inclusion criteria appropriate given the target population?
3. Are the treatment conditions for the patients appropriate?
4. Are the follow-up frequency and conditions appropriate?
5. Are the endpoints justified (relevant, feasible, accepted by the international community, etc.)?
6. Is the recording of adverse events appropriate?

Methodological validity and absence of bias

Regulatory concern is whether:

- will efficacy be real?
- will tolerance be underestimated?

I should review the following information

1. Is the method proposed (randomized trial, cohort, case-control study, etc.) appropriate for the research question? Is the randomization method appropriate and usable?
2. Is the calculation of the number of subjects to be included justified, bearing in mind the variability in measuring the primary endpoint and dropouts from the trial?
3. Are the trial and treatment dropout criteria accurate, appropriate, justified and verifiable?
4. Are criteria for terminating the trial well described and are they acceptable?
5. Is there a description of the broad outline of the planned statistical analysis

CRITICAL: Is there a description of the broad outline of the planned statistical analysis?

1. Choice of persons to be included in the analyses
   - with hypotheses regarding :
     - subjects lost to follow-up,
     - dropouts from treatment
2. Methods of accounting for missing or invalid data
3. Schedule of intermediate analyses
4. Management of amendments to the initial strategy analysis plan.

Feasibility of the trial as regards compliance with good practice

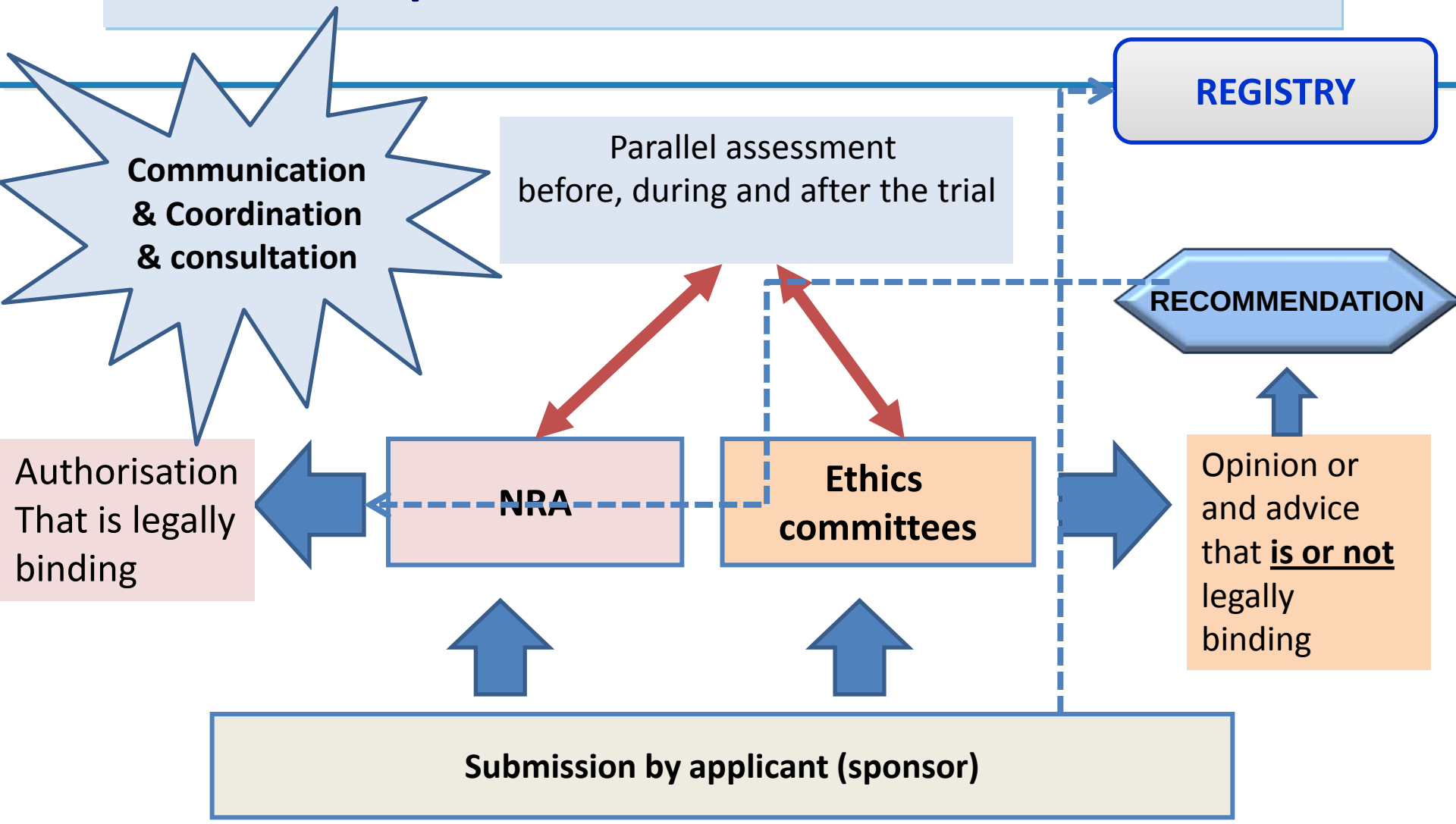
Regulatory concern is whether:

- is the trial possible under the conditions described into the protocol?

I should review the following information

1. Has the centre the capacity for the recruitment, care and follow-up of the subjects?
2. Products: is the planned product management and accountability satisfactory?
3. Laboratory samples: will the sampling and laboratory tests (biochemical analyses) be performed correctly?
4. Will the data collection and treatment procedure (analyses) be adequate?
5. Will the trial be monitored and subject to quality control (verification of data on site)?

Assessment process recommended for clinical trials



Guidelines and relevant regulation that needs to be used for performing regualtory oversight of clinical trials

Clinical trials guidance

GMP & GLP guidance

GCP guidance

Protection of subjects guidance

Transparency and accountability

Application submission

Regulations and Procedures

Ethics committee oversight

Quality of CT & investigational products

Safety: reporting of AEFIs and case management

Exchange of information and reporting

World Health Organization

Publication: European legislation
EudraLex - Volume 10 Clinical trials guidelines

http://ec.europa.eu/health/documents/eudralex/vol-10

- Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.
  - Chapter I: Application and Application Form
  - Chapter II: Monitoring and Pharmacovigilance
  - Chapter III: Quality of the Investigational Medicinal Product
  - Chapter IV: Inspections
  - Chapter V: Additional Information
  - Chapter VI: Legislation (directives)

Publications: World Health Organization (WHO)

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